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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,846	11/21/2005	Alexander Alan Morley	18857	8971

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,846	MORLEY ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13,15-17,28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13,15-17,28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 13, 15-17, 28, and 30-33 are pending and examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 07/08/2010.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is **FINAL**.

Withdrawn Claim Objections

1. The objections to claims 17 and 32, as set forth on page 3 of the Office Action of 01/08/2010, are **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 103

2. Claims 1, 2, 15-17, and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gattermann (1999) in view of Greiner et al (1995) (cited on PTO-892 of 12/31/2007).

Regarding independent claims 1, 2 and 17, Gattermann teaches clonality of mitochondrial DNA (mtDNA) sequences (e.g.: Fig. 2 and Fig. 4) in acquired idiopathic sideroblastic anemia (AISA) which is composed of non-neoplastic cells. Gattermann teaches (p.141 – The search for mtDNA mutations) that TGGE may be used to identify mtDNA mutations, where the method relies on heteroduplex formation between wild-type and mutant DNA, thus teaching co-localizations based on sequence identity, and

(Table 1) particular point mutations associated with AISA and other types of MDS, thus providing for qualitatively detecting levels of co-localized mtDNA. Gattermann teaches mutations associated woth phenotypes, thus providing for detecting (claim 1) and diagnosing (claims 2 and 17) pheotypes.

Relevant to claims 15 and 30, Gattermann teaches (p.145, left col.) TGGE, relevant to part (ii) of claims 15 and 30.

Relevant to claims 32 and 33, Gattermann teaches aspects of mutations generally associated with myelodsyplasia (e.g. Table 1).

Gattermann teaches aspects of mtDNA mutations associated with clonal expansion of non-neoplastic cells in myelodysplastic syndromes, but does not specifically exemplify detection of co-localized DNA to establish clonality (relevant to aspects of independent claims 1, 2 and 17), nor methods utilizing denaturing gels (claims 16 and 30). However, application of such methodologies in analysis of cellular clonality was well known in the art at the time the invention was made.

Relevant to independent claims 1, 2 and 17, Greiner et al teaches co-localizing nucleic acids derived from a subject (Fig. 2; p.49, right col., lns.1-25) in a gel-based analysis, and detecting the level of co-localization based on the presentation of a discrete band or a smear on a gel (Fig 5). Greiner et al thus provides an explicit teaching that co-localization higher than a background level is indicative of the presence of a clonal cell population (e.g: Fig 5; Fig 7; and p.47, right col., lns. 35-39).

Relevant to claims 16 and 30, Greiner et al teaches a DGGE analysis utilizing denaturing gel (e.g.: Fig 2; p.49).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods of Greiner et al for the analysis of non-neoplastic cell clonality, as taught by Gattermann. The skilled artisan would have been motivated to use the methods of Greiner et al because the skilled artisan would recognize that the methods of Greiner et al provide alternative methods for detecting clonality. Furthermore, the skilled artisan would be motivated by the teaching of Greiner et al that the methods disclosed by Greiner et al enhances resolution in the detection of clonal cell populations.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 over Gattermann (1999) in view of Greiner et al as set forth in the Office Action of 01/08/2010. Applicants' arguments (p.6-9 of Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Applicants have argued (p. 6 of Remarks) that where the claims recite 'co-localising mitochondrial DNA derived from a biological sample' (e.g.: claim 1), the claims are drawn to methods wherein said co-localising is 'the colocalization of a population of mitochondrial DNA exhibiting common acquired mutation'. However, the Examiner maintains that given the plain reading of the limitations of the claims, the claims are properly construed as requiring a step of (e.g.: as recited in claim 1) 'co-localising mitochondrial DNA', where such a recitation is properly construed as performing a step wherein the artisan practicing the method co-localises DNA (i.e. performs a step of placing DNA molecules in the same location as other DNA

molecules). Such an interpretation is consistent with, for example, dependent claim 30, which appears to further limit the steps by which a co-localization of DNA is performed. The claims as written do not recite, for example, 'determining that mitochondrial DNA molecules sharing a particular mutation are co-localized within a sample', where it may not even be proper for a claim to a method to have only a mental step of such determining.

Applicants have further argued (p.8 of Remarks) that Gatterman teaches that some types of clones (e.g. subclones of a clonogenic population) may not be detected with certain methods. However, there is nothing in the method as claimed, nor does there appear to be any particular contemplation in the specification as originally filed, for a requirement that particular subclones within a sample are detected, only that a clonal population may be detected. Further, where the claims are rejected in part over the teachings of Greiner et al, the Examiner maintains that the methods rendered obvious by the cited prior art as set forth in the instant rejection have no deficiencies with regard to different clonal populations that may be detected.

Applicants have argued (p.8-9 of Remarks) that the teachings of Greiner are not directed to any mitochondrial DNA mutations. The Examiner has used the teachings of Greiner only to provide that use of co-localization method steps (such as DGGE, as taught by Greiner) were well known in the art, and used in the analysis of clonality, at the time the invention was made.

The rejection as set forth is **MAINTAINED**.

3. Claims 13 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gattermann (1999) in view of Greiner et al (1995), as previously applied to claims 1, 2, 15-17 and 30-33, and further in view of Nomoto et al (2002) (cited on PTO-892 of 12/31/2009) and Sanchez-Cespedes et al (citation 1 on the IDS of 05/02/2008).

The teachings of Gattermann in view of Greiner et al are applied to claims 13 and 28 as they were applied to claims 1, 2, 15-17 and 30-33 previously in this Office Action.

Gattermann in view of Greiner et al does not specifically teach analysis of mitochondrial D-loop mutations in the analysis of clonality of non-neoplastic cells, as require by rejected claims 13 and 28. However, the application of D-loop mutation analysis to the detection of clonal populations of cells was well known in the art at the time the invention was made.

Nomoto et al teaches the analysis of clonal cell populations in cancer.

Relevant to the limitations of claims 13 and 28, Nomoto et al teaches the analysis of several polymorphic loci in the mitochondrial D loop (Table 1) to determine clonality of cancer cells (p.481 – Experimental design).

Additionally relevant to the obviousness of the methods of the instantly rejected claims, Sanchez-Cespedes et al teaches clonal selection of mitochondrial D loop sequences in normal tissue (Fig 3), and provides that D-loop alterations are present in normal cells and may achieve homoplasmy attributable to clonal expansion (p.7015 – Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the D loop sequences, as taught by both

Nomoto et al and Sanchez-Cespedes et al, in an analysis of MDS cell clonality by the methods rendered obvious by Gattermann in view of Greiner et al. One would have been motivated to examine D-loop sequences based on the teaching of Nomoto et al (p.481, right col., last ¶) that the high frequency of mutations in the control region of mitochondrial DNA provides a tool to determine the clonal origin of multiple cancers in individual patients, as well as the teachings of Sanchez-Cespedes et al that D-loop alterations are present in normal cells and may achieve homoplasmy attributable to clonal expansion (Abstract).

Response to Remarks

Applicants have traversed the instant rejection of claims under 35 USC 103 as obvious in view of the cited prior art. Applicants' arguments have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants have argued (p.9 of Remarks) that Nomoto teaches the identification of specific mutations in the detection of cancer. The Examiner maintains that Nomoto provide a teaching of the analysis of several polymorphic loci in the mitochondrial D loop (Table 1) to determine clonality of cancer cells (p.481 – Experimental design), which is particularly relevant to the instantly claimed methods; and as set forth in the rejection the prior art of Gatterman supplies the teaching of mitochondrial mutations use din the analysis of clonality in non-neoplastic cells. With regard to Applicants argument (p.9 of Remarks) that "the methodology of the present invention is highly sensitive and specific, being capable of detecting and differentiating mutations at different locations within the same region (D-loop), which represents a significant advantage over the prior

art, including the method disclosed in Gatterman, which admittedly would not detect a clonal subpopulation cells exhibiting a mitochondrial mutation", the Examiner maintains that there is nothing particular to the instantly claimed methods that requires detection and differentiating "mutations at different locations within the same region" of a mitochondrial sequence.

The rejection as set forth is **MAINTAINED.**

Withdrawn Double Patenting

4. The provisional rejection, on the ground of nonstatutory obviousness-type double patenting, of the instant claims over the claims of copending Application No. 11/587,740, as set forth on pages 8-9 of the Office Action of 01/08/2010, is **WITHDRAWN** in light of the amendments to the claims.

Conclusion

5. No claim is allowable or free of the teachings of the prior art.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634